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Safety of Ecklonia cava phlorotannins as a novel food pursuant to Regulation (EC) No 258/97

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Safety of *Ecklonia cava* phlorotannins as a novel food pursuant to Regulation (EC) No 258/97

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA),
Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean,
Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf,
Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka,
Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé,
Marco Vinceti, Peter Willatts, Karl-Heinz Engel, Rosangela Marchelli, Annette Pöting,
Morten Poulsen, Josef Rudolf Schlatter, Reinhard Ackerl and Henk van Loveren

Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the safety of *Ecklonia cava* phlorotannins (marketed as SeaPolynol™) as a novel food submitted pursuant to Regulation (EC) No 258/97. The novel food is a phlorotannin-rich alcohol extract of *Ecklonia cava*, which is an edible marine brown alga species. The information provided on the composition, the specifications, the production process and the batch-to-batch variability of the novel food is sufficient and does not raise safety concerns. The intention is to market the novel food as a food supplement for healthy individuals over the age of 12 years. A subchronic repeated dose oral toxicity study in rodents tested the novel food at daily doses of 0, 375, 750 and 1,500 mg/kg body weight (bw). The Panel considers the mid-dose as the no-observed-adverse-effect-level (NOAEL) of the study. Taking into account this NOAEL of 750 mg/kg bw per day and by applying an uncertainty factor of 200, the Panel considers an intake level of 3.75 mg/kg bw per day as safe. The Panel concludes that the novel food, *Ecklonia cava* phlorotannins, is safe for the use in food supplements at a maximum daily intake level of 163 mg/day for adolescents from 12 to 14 years of age, 230 mg/day for adolescents above 14 years of age and 263 mg/day for adults.

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Keywords: *Ecklonia cava*, brown alga, phlorotannins, novel food, safety

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Correspondence: nda@efsa.europa.eu

Panel members: Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Dominique Turck, Henk van Loveren, Marco Vinceti and Peter Willatts.

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Summary

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the safety of *Ecklonia cava* phlorotannins as a novel food (NF) submitted pursuant to Regulation (EC) No 258/97. The assessment follows the methodology set in Commission Recommendation 97/618/EC. The assessment is based on the data supplied in the original application, the initial assessment by the competent authority of Ireland, the concerns and objections of a scientific nature raised by the other Member States and the responses of the applicant.

The NF which is the subject of the application is an alcohol extract of *Ecklonia cava*, which is an edible marine brown alga species with a long tradition of food use in a number of Asian countries. The extract is rich in phlorotannins ($90 \pm 5\%$) and it is marketed under the trade name of SeaPolynol™. Phlorotannins are polyphenolic compounds found as secondary metabolites in certain brown algae species.

The information provided on the composition, the specifications, the production process and the batch-to-batch variability of the NF is sufficient and does not raise safety concerns.

The intention is to market the NF as a food supplement, with a proposed maximum daily intake of 360 mg. The target population for the NF is healthy individuals over the age of 12 years, with no other restrictions of use.

Based on the genotoxicity tests provided, the Panel notes that there is no evidence of genotoxicity for the NF.

The risk of allergic reactions to the NF is low.

A subchronic repeated dose oral toxicity study in rodents was provided, which tested the NF at daily doses of 0, 375, 750 and 1,500 mg/kg body weight (bw). The Panel considers the mid-dose, i.e. 750 mg/kg bw per day, as the no-observed-adverse-effect-level (NOAEL) of the study.

Taking into account the NOAEL of 750 mg/kg bw per day and by applying an uncertainty factor of 200 (composed of 100 to account for inter- and intraspecies variability, plus a factor of 2 to extrapolate from subchronic to chronic exposure), the Panel considers an intake level of 3.75 mg/kg bw per day as safe.

This level corresponds to 163 mg/day for adolescents from 12 to 14 years of age (mean bw of 43.4 kg), 230 mg/day for adolescents above 14 years of age (mean bw of 61.3 kg) and 263 mg/day for adults (default bw of 70 kg).

The Panel concludes that the NF, *Ecklonia cava* phlorotannins, is safe for the use in food supplements at a maximum daily intake level of 163 mg/day for adolescents from 12 to 14 years of age, 230 mg/day for adolescents above 14 years of age and 263 mg/day for adults.

The Panel notes that iodine intake from the NF may be of concern for people at risk of thyroid disease. The Panel also notes that intake of other food supplements containing iodine in addition to the NF might lead to iodine intakes above the upper level (UL).

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

On 14 May 2015, the company Botamedi Inc., Korea, submitted a request in accordance with Article 4 of the Novel Food Regulation (EC) No 258/97¹ to place on the market *Ecklonia cava* phlorotannins as a novel food (NF).

On 4 April 2016, the competent authority of Ireland forwarded to the Commission its initial assessment report, which came to the conclusion that an additional assessment is required in accordance with Article 6.3 of the Novel Food Regulation (EC) No 258/97.

On 10 May 2016, the Commission forwarded the initial assessment report to the other Member States (MS). The MS agreed with the initial assessment report made by the Food Safety Authority of Ireland and some of the MS included additional comments.

The concerns of a scientific nature raised by the MS can be summarised as follows:

- Regarding the specifications of the NF, there is some unclarity, in particular since a method of analysis (i.e. Folin–Ciocalteu method, using a polyphenol-dihydrate standard) was used for quantification of the phlorotannin content, which, according to the commenting MS, is prone to yield erroneous values.
- Concerns were raised on a significant proportion of not fully characterised phlorotannins present in the NF. Moreover, data on the absorption, distribution, metabolism and excretion (ADME) of phlorotannins in the human body were considered limited.
- The phloroglucinol in the NF might be broken down and release trihydroxybenzene monomers which may be of toxicological concern.
- The level of arsenic in the NF may pose a safety concern. The additional (i.e. in addition to the normal background diet) intake of arsenic via the NF may be significant and therefore may need to be lowered in the NF, in particular considering that the NF (in the form of a food supplement) might be consumed for extended periods of time.
- Given the high iodine content of the NF, such content should be indicated on the label of the NF in order to warn the consumer not to use the NF together with other food supplements and/or drugs high in iodine.
- The description of the extraction process was considered inadequate.
- Concerns were raised on the selection of the no-observed-adverse-effect-level (NOAEL) (i.e. mid-dose), since statistically insignificant but dose-related effects on body weight were observed also in the lower- and mid-dose groups.
- More information was required about the mode of action of the NF.
- One MS suggested considering a potential effect of the NF on glucose metabolism of diabetic individuals and people on anticoagulant therapy.
- One MS mentioned putative sleep-inducing effects of phlorotannins, claimed to have characteristics of GABAA-BZD receptor ligands (Cho et al., 2012).

In accordance with Article 29(1)(a) of Regulation (EC) No 178/2002², the European Food Safety Authority (EFSA) is asked to carry out the additional assessment for *Ecklonia cava* phlorotannins (marketed as SeaPolynol™) as a NF in the context of Regulation (EC) No 258/97.

EFSA is asked to carry out the additional assessment and to consider the elements of a scientific nature in the comments raised by the other MS.

2. Data and methodologies

2.1. Data

The assessment of the safety of the novel food (NF) is based on data supplied in the original application, the initial assessment by the competent authority of Ireland, the concerns and objections

¹ Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. OJ L 43, 14.2.1997, p. 1–6.

² Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.

of a scientific nature of the other MS and the responses of the applicant following requests for additional information.

In accordance with Commission Recommendation 97/618/EC,³ the NF, *Ecklonia cava* phlorotannins, is allocated to Class 2.2, i.e. a complex NF from non-GM source where the source has no history of food use in the Community. The data requirements for a NF of this class are the structured schemes I, II, III, IX, XI, XII and XIII, as stipulated by Commission Recommendation 97/618/EC. In the current scientific opinion, these structured schemes are listed in Sections 3.1–3.9. The intention is to market the NF in the form of food supplements. This assessment concerns only risks that might be associated with consumption of the NF under the proposed conditions of use, and is not an assessment of the efficacy of *Ecklonia cava* phlorotannins (SeaPolynol™) with regard to any claimed benefit.

2.2. Methodologies

The assessment follows the methodology set out in Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council.

3. Assessment

3.1. Specification of the NF

The NF which is the subject of the application is an alcohol extract of *E. cava*, which is an edible marine brown alga species. The extract is rich in phlorotannins ($90 \pm 5\%$) and it is marketed under the trade name of SeaPolynol™.

Phlorotannins are polyphenolic compounds found as secondary metabolites in certain brown algae species (such as *E. cava*). They are structurally different from land-based plant polyphenols (e.g. resveratrol, quercetin, epigallocatechin gallate) with the polymers/oligomers made of phloroglucinol (1,3,5-trihydroxybenzene).

The specifications of the NF are indicated in Table 1. They include the phlorotannin content of the NF as well as other chemical and physical parameters and specifications for contaminants such as heavy metals, microbiological specifications and impurities.

Table 1: Specifications of the NF

Parameter	Unit	Specification	Method
Phlorotannin	PGEQ% ^(a)	90.0 ± 5.0	Folin–Ciocalteu’s method
Dieckol	%	6.6–9.9	HPLC
Area Ratio BE cluster to Dieckol ^(b)	–	1.0–1.6	HPLC
Antioxidant activity	%	> 85	DPPH (reduction%, c = 0.1 mg/mL)
Moisture content	%	< 5	Moisture analyser
Ash	%	< 5	Direct ashing method
Insoluble substances ^(c)	–	negative	Dissolve and filtration method
Substances not originating from <i>E. cava</i> ^(d)	–	negative	Dissolve and filtration method Visual inspection
Appearance	–	brown powder	Visual inspection
Unpleasant odour or taste	–	negative	Sensory test
Viable cell count	CFU/g	< 3,000	3M Petrifilm method: PP-6406
<i>Staphylococcus aureus</i>	CFU/g	negative	3M Petrifilm method: PP-6424
Moulds and yeasts	CFU/g	< 300	3M Petrifilm method: PP-6417
<i>Salmonella</i> ssp.	CFU/25 g	negative	3M Petrifilm method: PP-6539
Coliforms	CFU/g	negative	Using BGLB media

³ Commission Recommendation 97/618/EC: Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council. OJ L 253, 16.9.1997, p. 1–36.

Parameter	Unit	Specification	Method
Lead (Pb)	mg/kg	< 3	ICP-MS
Mercury (Hg)	mg/kg	< 0.1	ICP-MS
Cadmium (Cd)	mg/kg	< 3	ICP-MS
Arsenic (As)	mg/kg	< 25	ICP-MS
Iodine (I ₂)	mg/kg	150.0–650.0	AOAC method: 932.21
Sieving size	mesh	> 60	Standard sieving method

HPLC: high-performance liquid chromatography; DPPH: 2,2-diphenyl-1-picrylhydrazyl; CFU: colony forming unit; BGLB: brilliant green lactose bile; ICP-MS: inductively coupled plasma mass spectrometry.

(a): Phloroglucinol equivalent using anhydrous phloroglucinol standard.

(b): BE cluster – cluster in chromatogram of 3 peaks consisting of 4 compounds:

2-O-(2,4,5-trihydroxyphenyl)-6,6'-bieckol, 6,6'-bieckol and 8,8'-bieckol + 7-phloroeckol.

(c): Originating from *Ecklonia cava* (e.g. non-soluble cellulosic residues).

(d): Any 'foreign' substance introduced erroneously during the manufacturing process.

In order to confirm that the manufacturing process is reproducible and adequate to produce on a commercial scale a product that is within the specifications as set above, the applicant provided batch-to-batch analyses (Table 2) for six batches of the NF.

Table 2: Batch-to-batch analysis of the NF

Parameter	Specification	Batch results of six commercial lots					
		20121124	20130425	20130827	20140408	20140410	20140728
Phlorotannin	90 ± 5% ^(a)	90.1	88.1	89.9	88.3	90.2	90.2
Antioxidant activity	> 85%	91.4	90.8	90.4	88.5	89.1	88.1
Moisture content	< 5%	1.8	3.2	4.7	3.2	2.5	2.6
Ash	< 5%	3.1	3.1	3.8	3.2	3.6	3.2
Insoluble substances ^(b)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
'Foreign' substances ^(c)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Appearance	Brown powder	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Unpleasant odour or taste	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Viable cell count	< 3,000 CFU/g	0	0	0	0	0	0
<i>Staphylococcus aureus</i>	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Moulds and yeasts	< 300 CFU/g	0	0	0	0	0	0
Coliforms ^(d)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Lead	< 3 mg/kg	1.32	1.82	2.81	1.53	1.52	1.67
Mercury	< 0.1 mg/kg	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Cadmium	< 3 mg/kg	0.08	0.12	0.156	0.13	0.08	0.14
Arsenic	< 25 mg/kg	21.30	16.56	21.69	21.49	23.40	19.81
Iodine	< 650 mg/kg	168.4	174.9	281.6	218.9	240.2	226.9
Sieving size	> 60 mesh	> 60	> 60	> 60	> 60	> 60	> 60

CFU: colony forming unit; n.d.: not detected.

(a): Phloroglucinol equivalent using anhydrous phloroglucinol standard (PGEQ).

(b): Originating from *Ecklonia cava* (e.g. non-soluble cellulosic residues).

(c): Any substance not originating from *Ecklonia cava* introduced erroneously during the manufacturing process.

(d): Coliform analysis covers *Escherichia coli*. Since no coliforms are present, the applicant considered that a specific method to distinguish *E. coli* from other coliforms is not necessary.

Proximate analysis showed that the sum of crude protein, crude fat, ash and moisture account for an average of 9.6 wt% of the NF. The amount of crude protein in the NF is approximately 2.2 wt% measured by the semimicro Kjeldahl method with a limit of detection (LOD) of ≥ 0.2 mg nitrogen (official method of the Korean Food Codex). The amount of phlorotannins in the NF is 90.0 ± 5.0 wt% as measured by a spectrophotometric Folin-Ciocalteu's assay using anhydrous phloroglucinol-dihydrate as the standard compound. The applicant also provided both HPLC- and $^1\text{H-NMR}$ -data confirming the presence of phlorotannins. The phlorotannins detectable with HPLC include dieckol, 8,8'-bieckol and 7-phloroeckol, 2-O-(2,4,5-trihydroxyphenyl)-6,6'-bieckol, 6,6'-bieckol, phlorofucofuroeckol-A, eckol, 2-phloroeckol, phlorotannin 974-A and 974-B, and fucofuroeckol with approximately 14.4 wt% with unknown structure. As not all phlorotannins are detectable by HPLC, the total unidentified phlorotannins amount to approximately 64 wt%. According to the applicant, the unidentified structures are considered to be open-chain polymers of phloroglucinol.

The level of inorganic arsenic in the NF according to three batch analyses is < 0.5 mg/kg. Considering the highest total arsenic amount of 23.40 mg/kg measured in the batch analyses, a daily dose of 360 mg of NF would contribute to 8.4 μg to the daily intake. This represents an additional 13.2% exposure to total dietary arsenic of < 64 μg per day estimated in the 2006 UK Total Diet Study (Rose et al., 2010).

The absence of residual ethanol was confirmed by the gas chromatographic method.

Analysis of six product batches for the presence of 245 pesticide residues, seven PCB congeners, and aflatoxins B1, B2, G1 and G2 were provided. Dioxins were detected only in one batch at 0.382 pg TEQ/g (with contribution to TWI 0.01%). Traces of two pesticides, azinphos-methyl (0.028 mg/kg in one sample) and phenthoate (0.162–0.442 mg/kg) were detected at low levels (to which the applicant has responded by deciding to change the harvest location to ensure the absence of pesticide residues).

The Panel notes that there is no indication for the production of toxins by *E. cava* or any other member of the order of the Laminariales.

The Panel considers that the information provided on the composition, the specifications and the batch-to-batch variability of the NF is sufficient and does not raise safety concerns.

3.1.1. Stability of the NF

Upon EFSA's request, the applicant provided data from a preliminary stability study showing that the phlorotannin content and the dieckol content of three commercial lots (packed in aluminium-polyethylene bags) of the NF were 99–100% and 97–100%, respectively, when stored at 25°C (RH 65%), 35°C (RH 75%), and 40°C (RH 75%) for 12 months. The phlorotannin content was measured by the Folin-Ciocalteu's method by using phloroglucinol-dihydrate as the standard compound. Dieckol was measured by HPLC (7.5–8 wt%). A second stability study on five commercial lots indicated that the NF is stable for 36 months at room temperature (25°C, RH 65%) as measured by the phlorotannin and dieckol contents.

The Panel considers that the data provided sufficient information with respect to the stability of the NF.

3.2. Effect of the production process applied to the NF

The manufacturing process of the NF is in accordance with Good manufacturing practice (GMP) standards and it takes into account the principles of Hazard Analysis and Critical Control Points (HACCP). The manufacturer is holder of an ISO 22000:2005 certificate.

Production begins with fresh, semidried *Ecklonia cava* seaweed, which is dried, crushed and subjected to alcohol (i.e. food-grade ethanol) extraction, purification, filtration and concentration steps. *E. cava* is abundant in southern Japan and South Korea, and the location of the seaweed source has been indicated as Jeju Island in South Korea. Each seaweed lot is visually inspected upon arrival for processing and undergoes quality analysis. A flow chart and detailed information on the manufacturing process have been provided.

The Panel considers that the production process is sufficiently described and does not raise concerns about the safety of the NF.

3.3. History of the organism used as a source of the NF

Ecklonia cava (Class: Phaeophyceae, Order: Laminariales, Family: Lessoniaceae) is a brown alga abundant in the seas (coasts) of central and southern Japan and South Korea. The use of brown algae

as a food can be traced back to the fourth century in Japan and the sixth century in China (McHugh, 2003). *E. cava* is consumed (in its natural form) as salad and in soups, but also in powder-form for the seasoning and colouring of, for instance, miso soup, rice cakes, candies and kimchi (traditional fermented Korean side dish). Upon EFSA's request to provide information on the amount of consumption of *E. cava*, the applicant argued that consumption data on specific species of seaweed are difficult to obtain. However, production data on Laminariales, which also includes *E. cava*, shows that 86,000–110,000 tonnes were produced yearly (2011–2015) in Japan. Including import of 48,000 tonnes (2013), it has been calculated that the amount of seaweed consumed daily per capita in Japan is 2.6 g (dry weight (dw)). For Korea, the amount of seaweed consumption per day and per capita is 5.2 g (dw).

The applicant also presented data on the use of *E. cava* as a source of alginates, which are used for various applications including food.

Phaeophyceae, which include *E. cava*, are a source for alginates authorised in the European Union (EU) as a food additive (E 400).

3.4. Anticipated intake/extent of use of the NF

The applicant intends to use the NF for inclusion in food supplements. The proposed maximum intake of the NF is 360 mg/day.

The target population for the NF is healthy individuals over the age of 12 years, with no other restrictions of use.

3.5. Information from previous human exposure to the NF or its source

The applicant has provided sales data (confidential) for food supplements and beverages containing the NF.

Food supplements containing *Ecklonia cava* phlorotannins have been sold in Japan and Korea since 2004. Since 2007 (Korea) and 2010 (Japan) 'high-dose' food supplements have been marketed, which provide 200–1200 mg *Ecklonia cava* phlorotannins per day.

In the USA, food supplements with *Ecklonia cava* phlorotannins have been sold since 2006, providing on average 100 mg of *Ecklonia cava* phlorotannins per day. In 2008, the *Ecklonia cava* extract was notified to the FDA as a new dietary ingredient, with a proposed daily dose of about 47 mg *Ecklonia cava* phlorotannins per day.

No adverse effects have been reported.

3.6. Nutritional information on the NF

Minerals are present in the NF in relatively high concentrations including sodium ($4,400 \pm 800$ mg/kg), calcium ($4,800 \pm 400$ mg/kg), magnesium ($1,300 \pm 100$ mg/kg), potassium (700 ± 200 mg/kg) and iodine (220 ± 40 mg/kg). In the upper range of iodine content as indicated in the specifications (up to 650 mg/kg), the proposed intake of the NF (360 mg) would lead to an iodine intake of 234 µg. In addition to iodine intake from food (excluding other food supplements), the total intake might exceed the reference value for iodine but will not exceed the upper level (UL; 450 µg for adolescents from 11 to 14 years, 500 µg for adolescents from 15 to 17 years and 600 µg for adults (SCF, 2002)). Taking into account the composition of the NF and the intended use level, the Panel considers that the consumption of the NF is not nutritionally disadvantageous.

3.7. Microbiological information on the NF

Microbiological specifications for the NF are presented in Table 1 (Section 3.1). The applicant provided analytical results for six batches of the NF, which were compliant with the microbiological specifications (Table 2, Section 3.1). Results for three additional batches were provided, which had been tested for the presence of *Salmonella* spp. Overall, the results show that yeast and moulds, coliforms (including *Escherichia coli*), *Staphylococcus aureus* and *Salmonella* are below the detection limit.

The Panel considers that the microbiological information provided for the NF does not raise safety concerns.

3.8. Toxicological information on the NF

The NF (SeaPolynol™) used in the following good laboratory practice (GLP) studies was manufactured according to the same raw material and extraction process and contains equivalent concentrations of phlorotannins ($92 \pm 7\%$, using the dihydrous phloroglucinol standard).

All studies were performed according to Korean regulations for Good Laboratory Practice and according to Korean Test Guidelines for Safety Evaluation of Drugs. If not mentioned otherwise, the design of the studies is comparable to corresponding OECD guidelines.

3.8.1. Absorption, distribution, metabolism and excretion

In a study on toxicokinetics (MPI Research Inc., 2013) provided by the applicant, groups of four male Sprague-Dawley [CrI:CD®(SD)] rats each received 10 mg/kg body weight (bw) of the NF (Lot 47-809) i.v., and 10, 100 and 1,000 mg NF/kg bw orally via gavage. Blood samples were collected pre-dose and at 15 and 30 min and 1, 2, 4, 6, 8, 12, 24 and 36 h post-dose and levels for the phlorotannins constituents dieckol, 8,8'-bieckol and phlorofucofuroeckol-A (PFF-A) in plasma were determined.

PFF-A was only detected after i.v. administration of 10 mg/kg bw and up to 1 h after oral administration of 1,000 mg/kg in a single rat and was much lower than for the other two components. While readily detectable after intravenous administration of 10 mg/kg bw, after gavage of 10 mg/kg bw NF bieckol and dieckol could also not be detected. In contrast to PFF-A, they could be detected after oral application of 100 and 1,000 mg/kg bw. For both, a more than proportional increase (factor 84 and 49 instead of 10) of the AUC from 100 to 1,000 mg/kg bw with dose is remarkable. Half-life periods for bieckol and dieckol ranged from 2.95 to 6.63 h and from 2.76 to 6.61 h for the two dose levels, respectively. Bioavailability following oral gavage administration was approximately 0.069–0.5% for 8,8' bieckol and 0.06–0.23% for dieckol.

Studies with polyphenols from other algae indicate glucuronidation and sulfation in the intestine (Corona et al., 2016). Furthermore, after passing the small intestine, the polyphenols are metabolised by the colonic microbiota into a wide range of low-molecular-weight phenolic acids that are absorbed and appear in the circulation after 6–24 h.

3.8.2. Genotoxicity

The applicant provided a bacterial reverse mutation test, an *in vitro* chromosome aberration test and an *in vivo* micronucleus test.

In the *in vitro* bacterial reverse mutation test (Biototech Co. Ltd., 2006a), the NF was tested in the *Salmonella* Typhimurium strains (TA98, TA100, TA1535 and TA1537) and *E. coli* (WP2uvrA(pKM101)) strains without and with metabolic activation system (S9 mix). The number of revertant colonies was not increased with and without metabolic activation up to 5,000 µg/plate. No cytotoxicity was observed.

In the *in vitro* chromosome aberration test (Biototech Co. Ltd., 2006b) in Chinese hamster lung cells (CHL/IU), the NF was tested with concentrations up to 290 µg/mL, which was the IC₅₀ (inhibition concentration 50%) in a pre-test. The number of cells with structural chromosome aberrations was not increased by the NF as compared with the negative control group, in the presence or absence of metabolic activation system in both the short time and continuous treatment. In the positive control group, the number of cells with structural chromosome aberration was significantly increased as compared with the negative control group.

In a pre-test for an *in vivo* micronucleus test (Biototech Co. Ltd., 2006c), 2,000 mg/kg bw NF (Lot No. LC-SP-20060626; tannin content $\geq 95\%$) was administered once by gavage to three male CrIj:CD1(ICR) mice per group and the bone marrow (2,000 erythrocytes) was checked for the frequency of micronuclei, after 24, 48 and 72 h. There was no increase in the frequency of micronuclei in any of the time points. In the main test, five male mice per group received via gavage 500, 1,000 and 2,000 mg/kg body weight. After 24 h, the frequency of micronucleus induction was determined per 2,000 erythrocytes. There was no significant difference in the frequency of micronucleated polychromatic erythrocytes (MNPCE) for all treatment groups compared with that of the negative control. The polychromatic erythrocytes (PCE)/(PCE + normochromatic erythrocytes (NCE)) ratio was not significantly different between treatment groups and control groups. In conclusion, the test substance (i.e. the NF) did not induce micronucleus formation in bone marrow cells in mice. The Panel notes that even though the group of parent compounds (i.e. phlorotannins) in the NF are unlikely to reach the bone marrow, the

metabolically produced phenolic compounds therefrom can be expected to be absorbed and reach the bone marrow. This assumption is further corroborated by systemic effects in the subchronic toxicity study (Section 3.8.5), which suggests systemic availability of the NF and/or its metabolites.

The Panel notes that there is no evidence of genotoxicity for the NF.

3.8.3. Acute toxicity studies

In an acute toxicity study (Biototech Co. Ltd., 2007a) provided by the applicant, 10 male and 10 female Sprague–Dawley (CrI:CD(SD)) rats were administered once orally by gavage 2,000 mg NF/kg bw. Findings in the 14 days observation period were soft stools, diarrhoea, mucous stools, compound-coloured faeces and soiled perineal region from the day of administration until day 2. No mortalities occurred.

In a second study (Biototech Co. Ltd., 2007b), two male and two female Beagle dogs were administered the NF in capsules at intervals of 4 days, i.e. day 0: 100 mg/kg bw, day 4: 300 mg/kg bw and day 8: 1,000 mg/kg bw. Two male and two female dogs served as controls. After the last application, there was a 2-week observation period. Compound-coloured stools were observed in all males and females treated with 300 and 1,000 mg/kg bw. Vomiting was observed in one male and one female dog receiving 1,000 mg/kg bw. No mortalities occurred.

3.8.4. Subacute toxicity studies

In a dose-range finding study (Biototech Co. Ltd., 2010a) for a subchronic toxicity study, five male and five female Sprague–Dawley (CrI:CD(SD)) rats per group were administered the NF by gavage at doses of 0, 500, 1,000 and 2,000 mg/kg bw once daily in water for 4 weeks. Compound-coloured stools were evident in all males and females in the dosing groups from day 1 during the dosing period. Salivation after dosing was evident sporadically in one female at 1,000 mg/kg bw and in two males and two females at 2,000 mg/kg bw from days 5 to 17 during the dosing period. In clinical chemical investigations at 2,000 mg/kg bw per day, statistically significant increases in alanine aminotransferase (ALT), and decreases in total protein, triglycerides and glucose were detected in male rats. In addition, absolute and relative liver weights and absolute kidney weights were statistically significantly increased in males at 2,000 mg/kg bw per day. In female rats, relative heart weights were decreased statistically significantly at 1,000 and 2,000 mg/kg bw per day. There were no statistically significant differences between the study groups concerning body weight. Histopathologically, atrophy of periportal hepatocytes in the liver was detected in male rats at 2,000 mg/kg bw per day.

In another study (Yeo et al., 2012), which was an efficacy study, mice (7 weeks of age, 10 mice per group) were fed a diet containing an increased amount of fat, i.e. 20%, as compared to 5–10% in usual rodent diets. After 1 week, the animals received in addition each day 0, 1.25, 2.5 and 5 mg/mouse of the NF orally for further 3 weeks. These dosages correspond to 27, 54 and 135 mg NF/kg bw per day. An additional group was fed a diet without fat, and there were also groups receiving various amounts of dieckol, one of the major phlorotannins in the NF. At the end of the study, there was a dose-related lower body weight of about 12–16% in the animals receiving the NF compared to control. Triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol were decreased in all dose groups. Liver enzymes (glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT)), blood urea nitrogen (BUN) and creatinine values in serum were not affected. No data on food consumption were provided.

3.8.5. Subchronic toxicity studies

A subchronic toxicity study (Biototech Co. Ltd., 2010b) in rodents was provided by the applicant. In this study, 10 male and 10 female Sprague–Dawley (CrI:CD(SD)) rats were administered by gavage for 13 weeks the NF once daily in water at doses of 0, 375, 750 and 1,500 mg/kg bw. In order to assess the reversibility of potential effects, five additional animals per sex for the control and the high-dose group were investigated after a 4-week recovery period.

Compound-coloured stools occurred at all dose levels. These compound-coloured stools were likely caused by excretion of the test substance and were thus not considered to be of toxicological significance.

At a dose of 750 mg/kg bw per day and above, BUN was statistically significantly decreased in males, glucose was statistically significantly decreased in females and neutrophil counts were significantly increased in females, compared to controls. In addition, sporadic salivation occurred in females.

At a dose of 1,500 mg/kg bw per day, incidence of salivation in females increased and it occurred also in male rats. Salivation was mainly observed after gavage, but to some degree also before. It was considered by the authors of the study to be a temporary sign caused by the test substance, since it was no longer evident in the afternoon. The number of animals with salivation increased with study duration.

At 1,500 mg/kg bw per day, males and females receiving the NF had a lower body weight (11.7% and 8.7%, respectively) at the end of the study compared to control animals even though differences were not statistically significant. This effect was dose related, appearing to a minor degree also at the lower dose levels. Effects on body weight were even more pronounced in the recovery group in both sexes. Food consumption, however, was not decreased. Blood chemistry analyses showed significant increases of phosphorus and ALT concentrations in males, a significant decrease of triglycerides in males and a significant decrease of glucose in females receiving 1,500 mg/kg bw per day, compared to controls. In addition, prothrombin time was statistically significantly increased in males compared to controls. These changes were not evident during the recovery. There were no compound related findings in histopathological investigations including the liver.

The Panel considers that the salivation observed after administration of the NF may be due to bad taste/astringent properties which may not be tolerated even with minor amounts of test substance during gavage. It is considered to be rather concentration than dose-dependent.

The Panel notes that at a dose of 1,500 mg/kg bw per day, in addition to the lower body weight (which, although not statistically significant, was taken by the authors of the study as the lowest-observed-adverse-effect-level (LOAEL)), ALT and prothrombin time were increased, while BUN was decreased as compared to controls. These findings may indicate liver toxicity, which has been confirmed histopathologically at higher dose levels in the 28-day study.

The Panel considers that the statistically significant findings in the mid-dose group are small, only found in one gender, are within normal ranges (neutrophils), might be related to metabolic effects (BUN and glucose) owing to a lower body weight gain, and are, thus, not considered adverse.

The Panel, therefore, considers the mid-dose, i.e. 750 mg/kg bw per day, as the NOAEL of the study.

3.8.6. Human studies

The applicant provided four published human studies (Oh et al., 2010; Lee et al., 2012; Shin et al., 2012; Choi et al., 2015) which were performed with *Ecklonia cava* phlorotannins. For the publication by Choi et al. (2015), the applicant provided the unpublished study report by Park and Choi (2012).

A double-blind, placebo-controlled, crossover study was conducted by Oh et al. (2010) in order to assess an acute effect of (pre-exercise) *Ecklonia cava* phlorotannin supplementation on endurance performance in 20 male college students during highly intense exercise. The Panel considers that no conclusions can be drawn from this acute efficacy study for the safety assessment of the NF.

Lee et al. (2012) conducted an uncontrolled open-label, single-arm study to assess the effect of *Ecklonia cava* phlorotannins in 52 individuals with hypercholesterolaemia (fasting total cholesterol concentration > 240 mg/dL or LDL cholesterol concentration > 130 mg/dL). The prevalence of hypertension and diabetes mellitus in the sample was 23.4% and 8.7%, respectively. All subjects consumed daily 400 mg of *Ecklonia cava* phlorotannins (Lot No. SP-20081216; phlorotannin content 98.5% (PGDEQ)). Haematological, clinical chemical parameters as well as urinalysis did not indicate adverse effects. One case (2.2%) each of nausea, dyspepsia, diarrhoea and alopecia was reported.

Shin et al. (2012) conducted a 12-week randomised, double-blind, three-arm parallel trial in 107 overweight (BMI: 24–29 kg/m²) Korean men and women to assess the effects of *Ecklonia cava* phlorotannins on anthropometric and blood lipid parameters. Subjects were randomly distributed to one of the following three study groups: (i) placebo, (ii) 72 mg/day *Ecklonia cava* phlorotannins or (iii) 144 mg/day *Ecklonia cava* phlorotannins (Lot No. SP-20080510; phlorotannin content 98.5% (PGDEQ)). The study enrolled 107 subjects (69 women and 38 men) between 19 and 55 years of age, of which 97 subjects completed the trial. No power calculations were provided. Differences over time and between treatments were determined using two-factor analysis of variance (ANOVA) with repeated measures. There were no noticeable signs of adverse events related to ingestion of the supplement, and a panel of routine serum clinical chemistries and haematological parameters, which included WBC counts, remained within normal ranges during the intervention period.

A randomised, double-blind, placebo-controlled trial (Choi et al., 2015; unpublished study report by Park and Choi, 2012) with the NF was conducted in subjects with hyperlipidaemia (total cholesterol > 200 mg/dL or LDL cholesterol > 110 mg/dL). A total of 80 men and women between 19 and 80 years

were enrolled. Study participants ingested 400 mg/day of the NF (Lot No. SP-20101012; phlorotannin content 98.2% (PGDEQ)) or a placebo for 12 weeks. Two subjects (one from each group) discontinued the study because they had withdrawn their consent. Two participants in the placebo group were excluded from the analyses due to lack of compliance. Thirteen participants (6 and 7 subjects from the NF and placebo group, respectively) were excluded from the analyses because of their family history in hyperlipidaemia, resulting in 63 subjects who were included for the primary and secondary endpoint analysis. For the safety assessment, all the enrolled subjects ($n = 80$) were considered. Sample size power calculations were based on total cholesterol levels in the test and placebo group after 12 weeks of 10.1 and 5.6 mg/dL, respectively, with a standard deviation (SD) of 7.2 mg/dL in both groups. It was calculated that for a power of 80% with a 2-tailed alpha of 0.05, a total of eighty subjects were needed, allowing for a 20% dropout rate. Differences between groups were analysed using a linear mixed-effects model. No differences were seen between the study groups regarding the concentration of liver enzymes (ALT and aspartate transaminase (AST)). There were 10 cases (in 8 subjects, 4 per study group) of mild adverse events that were not considered related to consumption of the test product. Statistically significant differences were seen between the groups for white blood cell counts and high-sensitive C-reactive protein (hs-CRP). However, the observed differences were small, remained within normal ranges and might have resulted from apparent differences between study groups at baseline. Therefore, the Panel considers these findings not to be of clinical relevance.

3.8.7. Other studies

One MS expressed concerns as to claimed sleep-inducing effects of phlorotannins in *E. cava* as investigated in the animal study by Cho et al. (2012). In this study, an ethanol extract of *E. cava* administered (p.o.) at doses up to 1,000 mg/kg bw to mice treated with pentobarbital (i.p.) increased sleep duration and decreased sleep latency when compared to control. Administration of the extract alone, i.e. without pentobarbital, did not induce sleep. The Panel notes that in this study the administration of an ethanol extract of *E. cava* at 1,000 mg/kg bw did not induce sleep in mice. The Panel also notes that in the 90-day oral toxicity study (Section 3.8.5), which was performed with doses up to 1,500 mg/kg bw per day, no evident behavioural changes in the studied animals were reported.

3.9. Allergenicity

The NF contains on average 2.2% protein. The applicant performed a literature search in databases such as AllergenOnline, Pubmed, Scopus and Web of Science, in order to retrieve any information on a positive relationship between *E. cava* and allergenicity. The applicant also considered history of traditional use and information from current commercial consumption of the NF and clinical trials performed with *Ecklonia cava* phlorotannins. The applicant did not identify any evidence of allergenicity to *E. cava*. Furthermore, the applicant states that the US and Asian distributors of *Ecklonia cava* phlorotannin-containing food supplements (i.e. SeaPolynol™) have adverse event reporting procedures in place and that to date allergic reactions to the NF have not been reported.

The Panel considers that the risk of allergic reactions to the NF is low.

4. Discussion

The NF which is the subject of the application is a phlorotannin-rich ($90 \pm 5\%$) alcohol extract of the edible brown alga *E. cava*.

The information provided on the composition, the specifications, the production process and the batch-to-batch variability of the NF is sufficient and does not raise safety concerns.

Brown algae, including *E. cava*, have a long tradition of food use in a number of Asian countries. Food supplements containing *Ecklonia cava* phlorotannins are being sold in Japan, Korea and the USA.

The intention is to market the NF as a food supplement, with a proposed maximum daily intake of 360 mg. The target population for the NF is healthy individuals over the age of 12 years, with no other restrictions of use.

The Panel notes that there is no evidence of genotoxicity for the NF.

A subchronic toxicity study was provided, which tested the NF in rodents at daily dosages of 0, 375, 750 and 1,500 mg/kg bw. The Panel considers the mid-dose, i.e. 750 mg/kg bw per day, as the NOAEL of the study.

Taking into account the NOAEL of 750 mg/kg bw per day and by applying an uncertainty factor of 200 (composed of 100 to account for inter- and intraspecies variability, plus a factor of 2 to extrapolate

from subchronic to chronic exposure (EFSA Scientific Committee, 2012)), the Panel considers an intake level of 3.75 mg/kg bw per day as safe.

This level corresponds to 163 mg/day for adolescents from 12 to 14 years of age (mean bw of 43.4 kg), 230 mg/day for adolescents above 14 years of age (mean bw of 61.3 kg) and 263 mg/day for adults (default bw of 70 kg) (EFSA Scientific Committee, 2012).

The Panel notes that iodine intake from the NF may be of concern for people at risk of thyroid disease.

The Panel also notes that intake of other food supplements containing iodine in addition to the NF might lead to iodine intakes above the UL.

5. Conclusions

The Panel concludes that the NF, *Ecklonia cava* phlorotannins, is safe for the use in food supplements at a maximum intake level of 163 mg/day for adolescents from 12 to 14 years of age, 230 mg/day for adolescents above 14 years of age and 263 mg/day for adults.

Steps taken by EFSA

- 1) Letter from the European Commission to the European Food Safety Authority with the request for a scientific opinion on the safety of *Ecklonia cava* phlorotannins. Ref. Ares(2016) 3833320, dated 22 July 2016.
- 2) On 4 August 2016, EFSA received the following documentation: dossier 'Conf. SeaPolynol 29.04.15', submitted by Botamedi Inc., Korea; initial assessment report ('SeaPolynol Initial Assessment 2182192') carried out by the Food Safety Authority of Ireland; Member States' comments and objections; response by the applicant to the initial assessment report and the Member States' comments and objections.
- 3) On 16 September 2016, EFSA sent a request to the applicant to provide missing information to accompany the application.
- 4) On 23 September 2016, EFSA received the missing information as submitted by the applicant. After checking the content of the full dossier, including the newly submitted information, EFSA considered the application valid as of 29 September 2016.
- 5) On 2 March 2017, EFSA sent a request to the applicant to provide additional information to accompany the application.
- 6) Additional data were provided by the applicant on 28 April 2017.
- 7) On 8 June 2017, EFSA sent a request to the applicant to provide additional information to accompany the application.
- 8) Additional data were provided by the applicant on 6 July 2017.
- 9) During its meeting on 20 September 2017, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of *Ecklonia cava* phlorotannins as a novel food pursuant to Regulation (EC) No 258/97.

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Abbreviations

ADME	absorption, distribution, metabolism and excretion
ALT	alanine transaminase
ANOVA	analysis of variance (ANOVA)
AST	aspartate transaminase
AUC	area under the curve
BGLB	brilliant green lactose bile
BUN	blood urea nitrogen
bw	body weight
CHL	Chinese hamster lung
DPPH	2,2-diphenyl-1-picrylhydrazyl
dw	dry weight
GLP	good laboratory practice
GMP	good manufacturing practice
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
¹ H-NMR	proton nuclear magnetic resonance
HACCP	Hazard Analysis and Critical Control Points
HPLC	high-performance liquid chromatography
hs-CRP	high-sensitive C-reactive protein
IC ₅₀	inhibition concentration 50%
ICP-MS	inductively coupled plasma mass spectrometry
i.p.	intraperitoneal
i.v.	intravenous

LDL	low-density lipoprotein
LOAEL	lowest-observed-adverse-effect-level
LOD	limit of detection
MNPCE	micronucleated polychromatic erythrocytes
MS	Member State
NCE	normochromatic erythrocytes
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NF	novel food
NOAEL	no-observed-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
p.o.	per os
PCE	polychromatic erythrocytes
PFF-A	phlorofucofuroeckol-A
RH	relative humidity
UL	upper level
WBC	white blood cell